ODAC Discussion on Accelerated Approval
08 February 2011

Erbitux®
(cetuximab)

Erbitux in the treatment of metastatic colorectal carcinoma (mCRC)

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on behalf of
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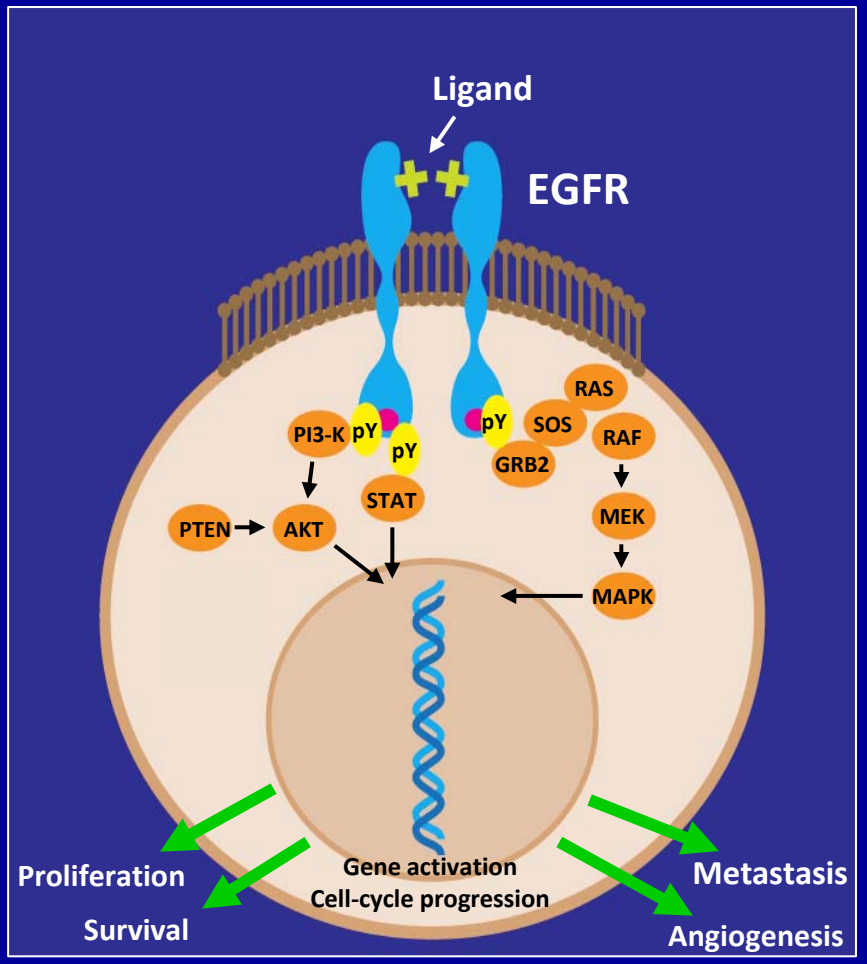
Importance of Accelerated Approval

- Accelerated approval is an important path for oncology drug development.
- New drugs approved under accelerated approval for use in patients with mCRC played role in rapid advances in treatment.
- Frequent interaction with FDA is essential if accelerated approval is planned including agreement on confirmatory studies.

Introduction

- Erbitux is a chimeric IgG1 monoclonal antibody.
- Binds specifically to EGFR and its heterodimers with higher affinity than natural ligands.
- Prevents ligand binding to EGFR and subsequent signal transduction; down-regulates EGFR.

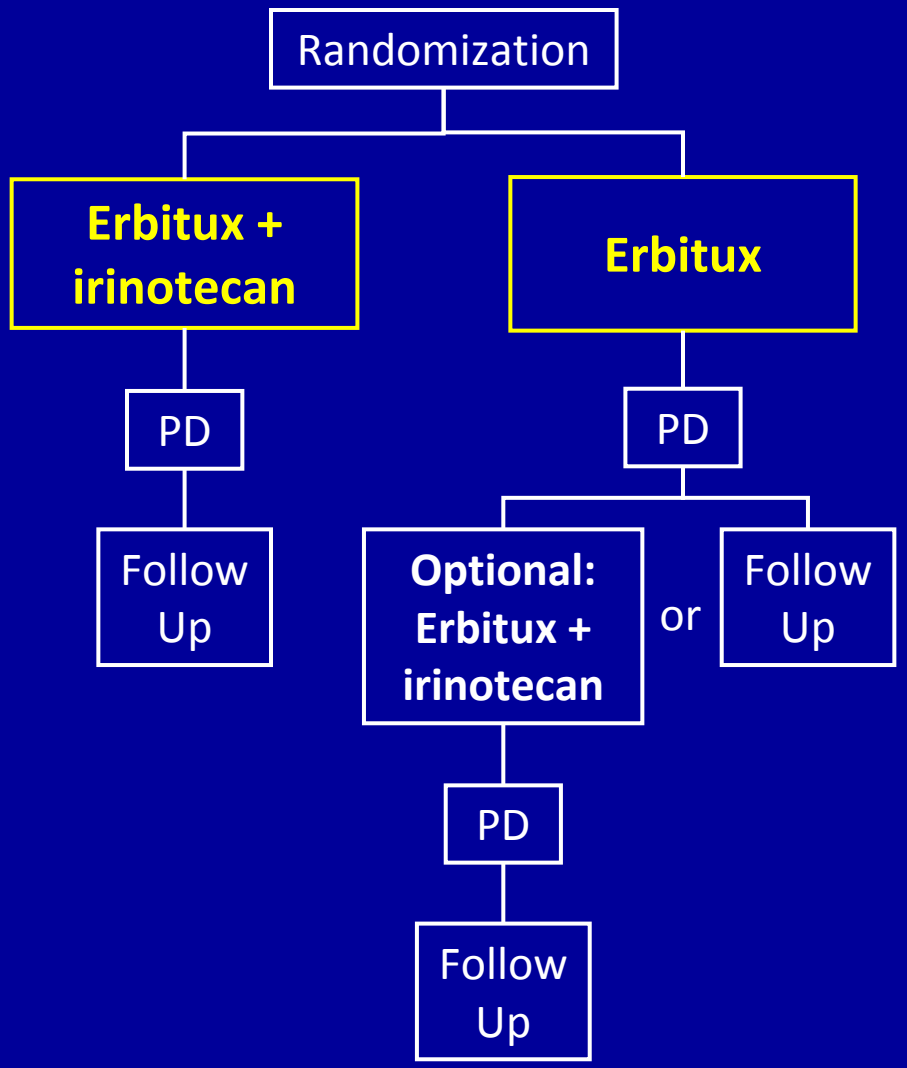


Approved Indications

- Accelerated approval as a single agent and in combination with irinotecan in patients with mCRC refractory or intolerant to irinotecan (2004)
  - Regular approval as a single agent in patients with mCRC after failure of prior therapies (2007)
  - Restriction in mCRC: not recommended for the treatment of CRC in patients with *K-Ras* mutant tumors (2009)
- Regular approval in combination with radiation therapy and as single agent in patients with locally advanced HNC (2006)

Erbitux has demonstrated clinical benefit in multiple solid tumors.

Pivotal Study Supporting Accelerated Approval (Study EMR 62 202-007 [BOND])



- Phase 2, randomized, open-label, multicenter study
- Primary objective: ORR
- Key secondary objective: TTP, DOR, and safety
- EGFR+ mCRC
- Disease progression on prior irinotecan therapy
- N = 300

BOND Study Results

	Erbitux + irinotecan (N=218)	Erbitux (N=111)	HR	p-Value
ORR	22.9%	10.8%	--	0.007
DOR	5.7 mo	4.2 mo	--	--
TTP	4.1 mo	1.5 mo	0.54	<0.001

Abbreviations: DOR = duration of response; HR= hazard ratio; ORR = objective response rate; TTP = time to progression.

Erbitux is an active agent in mCRC.

Cunningham D, et al. *N Eng J Med* 2004;351:337-345.

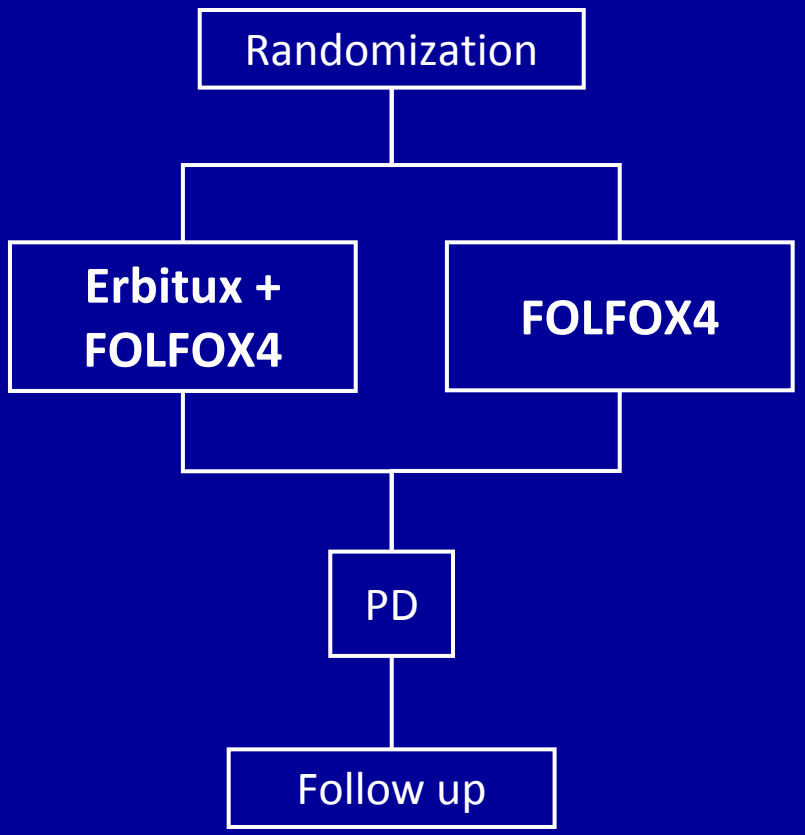
Accelerated Approval Required PMCs

The Sponsor agreed to complete the following PMCs to confirm clinical benefit and convert accelerated approval to regular approval:

- **PMC 1:** *To complete Protocol CA225-006 (EPIC), A Phase III, randomized, open-label, multicenter study of irinotecan and cetuximab versus irinotecan as second-line treatment in patients with metastatic, EGFR-positive colorectal carcinoma*

- **PMC 2:** *To complete Protocol CA225-014, A Phase III, randomized, multicenter study of cetuximab, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin versus oxaliplatin, 5-FU, and leucovorin in patients with previously treated metastatic EGFR-positive colorectal carcinoma*

PMC 2: Study CA225-014



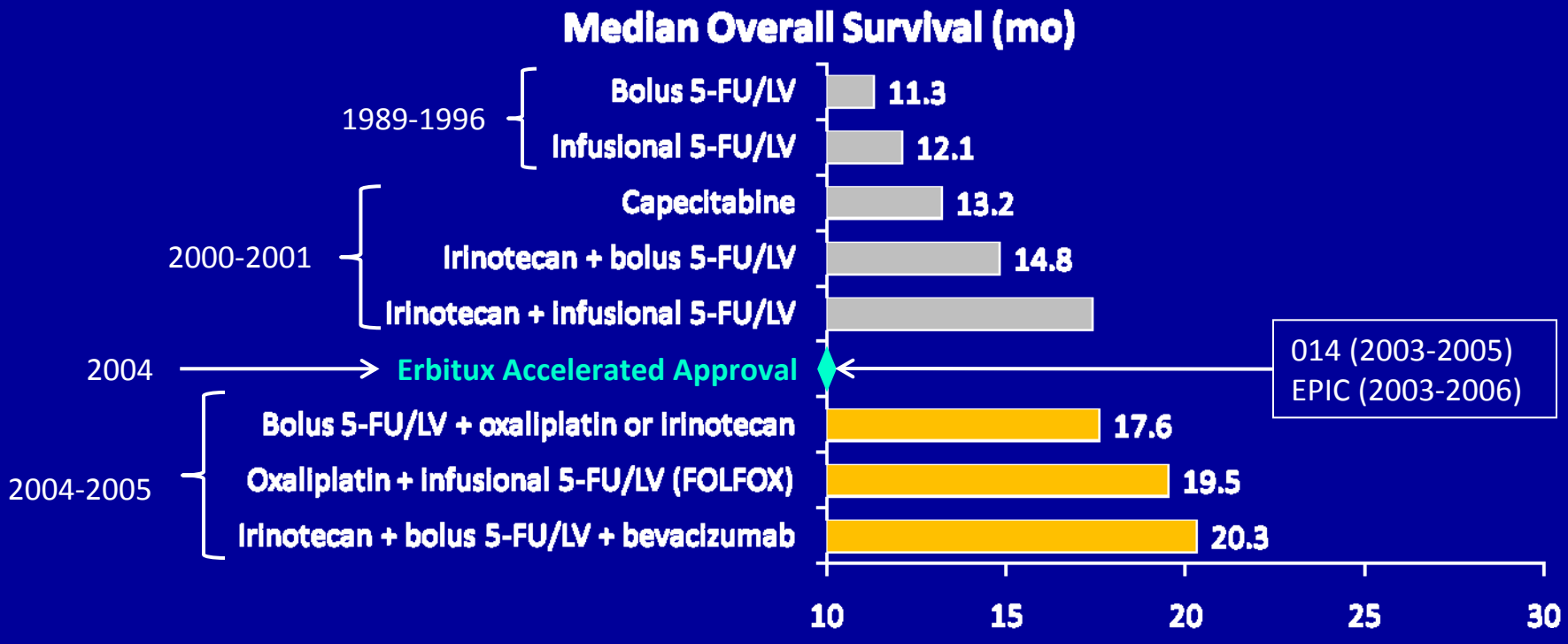
- Phase 3, randomized, open-label, multicenter study
- Primary objective: OS
- Key secondary objectives: PFS, RR, and safety
- EGFR+ mCRC
- Prior irinotecan-containing regimen as 1st-line treatment of mCRC
- N = 1100
- Initiated in Mar 2003

Challenge: New Drug Approvals

- Significant changes in SOC for treatment of mCRC:
  - Oxaliplatin approved 09 Jan 2004
  - Cetuximab approved 12 Feb 2004
  - Bevacizumab approved 26 Feb 2004

Multiple new drugs for the treatment of mCRC approved in 2004 lead to changes in SOC.

Evolution of 1st-Line mCRC Therapies



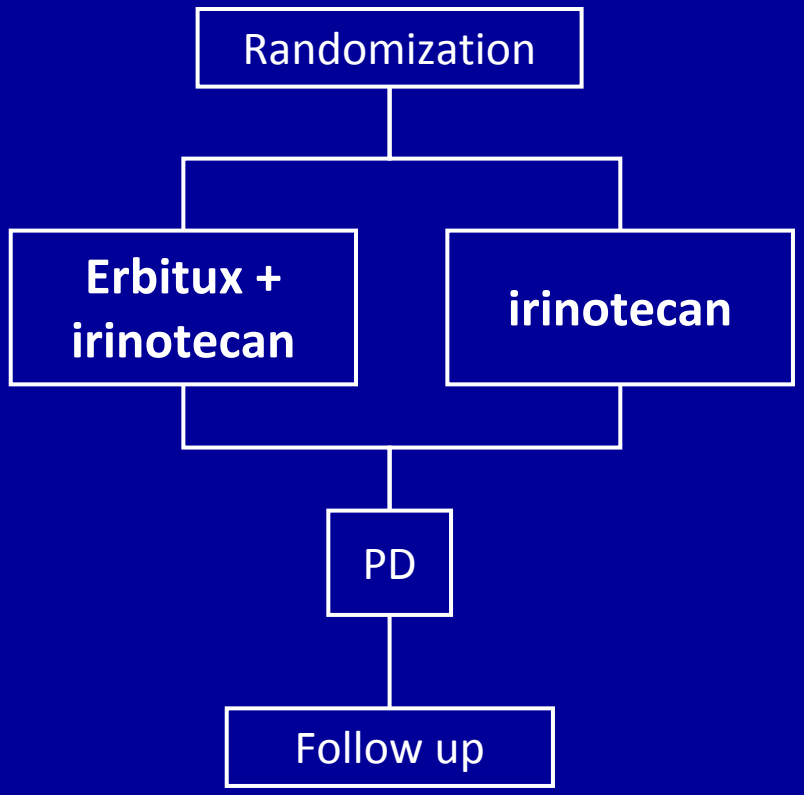
Rapid adoption of new treatment in the US made recruitment to the Study 014 clinical trial difficult.

Interactions with FDA for PMC 2 Study CA225-014

- Sponsor provided data package concerning impact of change in SOC on patient accrual on 15 Nov 2004.
- FDA released the Sponsor on 10 Jan 2005 because PMC 2 study enrollment was no longer feasible.

Due to rapid change in standards of care, enrollment of patients in Study 014 study was no longer feasible.

PMC 1: EPIC Study Design



- Phase 3, randomized, open-Label, multicenter study
- Primary objective: OS
- Key secondary objectives: PFS, ORR, and safety
- EGFR+ mCRC
- Prior oxaliplatin + fluoropyrimidine for 1st-line mCRC
- N = 1300

PMC 1: EPIC Milestones

Study was initiated in May 2003 and was ongoing at time of accelerated approval.

Milestone	Commitment	Completed	On Time
Patient accrual completed	30 Jun 2005	07 Feb 2006	
Study completion (Data Cut Off)	31 Dec 2006	28 Jun 2006	✓
Submit final study report	30 Jun 2007	27 Jun 2007	✓

Sponsor was diligent in completing EPIC Study.

PMC 1: EPIC Study Results (ITT)

	Erbitux + irinotecan (N=648)	irinotecan (N=650)	HR	p-Value
OS	10.7 mo	10.0 mo	0.98	0.71
PFS	4.0 mo	2.6 mo	0.69	<0.0001
ORR	16.4%	4.2%	--	<0.0001

Abbreviations: HR = hazard ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Erbitux showed activity but did not demonstrate improvement in OS.

Sobrero AF, et al. *J Clin Oncol* 2008;26:2311-19.

Challenge: Availability of Erbitux

- Availability of Erbitux following accelerated approval may have contributed to EPIC nonsignificant OS result:
  - Erbitux became available and rapidly adopted in the refractory population.
  - 41% of patients in the control arm received treatment with of Erbitux + irinotecan following disease progression.

Post-study Erbitux + irinotecan treatment may have confounded EPIC OS result.

Interactions with FDA Regarding PMC 1 EPIC Study

- EPIC results were discussed with FDA in Dec 2006. FDA concluded that:
  - EPIC results were not adequate to fulfill PMC 1.
  - OS was required to confirm the clinical benefit of Erbitux for patients with mCRC.
- The Sponsor discussed two additional phase 3 studies to support demonstration of clinical benefit:
  - CA225-025
  - CRYSTAL

Additional studies that could demonstrate clinical benefit of Erbitux discussed with FDA.

Discussion of Study CA225-025 with FDA

- Phase 3 study of Erbitux + BSC versus BSC
  - Primary objective: OS
  - OS Results: HR=0.766, p-value 0.0046
- FDA granted regular approval for Erbitux single agent based on positive OS results for Study CA225-025 in Oct 2007.
- FDA required additional studies to confirm the clinical benefit of Erbitux in combination with irinotecan for patients with mCRC.

CA225-025 confirmed clinical benefit of Erbitux as a single agent in patients with mCRC.

Challenge: Changes in Science Predictive Biomarker

- Role of *K-Ras* in predicting efficacy of Erbitux in mCRC had not been established at time of EPIC study initiation and reporting of results.
  - Potential signal for use of *K-Ras* as a predictive biomarker emerged in 2007.
- *K-Ras* data from 5 Erbitux mCRC studies was submitted to FDA in Apr 2008.
- *K-Ras* data presented at ASCO 2008
  - Ongoing clinical trials amended to incorporate *K-Ras* testing.
  - Guidelines recommend *K-Ras* testing.
- FDA convened an ODAC on biomarkers, using *K-Ras* as an example, in Dec 2008.

Emerging data identified *K-Ras* as a predictive marker in selecting patients most likely to benefit from anti-EGFR mAb treatment.

Regulatory Pathway Enabling Fulfillment of PMC 1

- In Dec 2008, ODAC discussed a framework to support evaluation of safety and efficacy based on emerging biomarkers.
  - A framework for prospective – retrospective analysis was developed.
- The ODAC discussion afforded the opportunity to work with the FDA to find a path forward for PMC 1.
  - Framework applied in Erbitux mCRC studies.

A regulatory framework based on prospective-retrospective analysis enables a path forward.

Study EMR-62202-013 [CRYSTAL]

- Phase 3, randomized, open-label, multicenter, controlled study comparing Erbitux in combination with FOLFIRI versus FOLFIRI alone in 1st-line mCRC.
  - Primary objective: PFS (ITT)
  - Key secondary objectives: OS, ORR, safety, and QoL
- 89% (N=1063) sample ascertainment rate for *K-Ras* testing
- For PFS, OS, and ORR, Erbitux in combination with FOLFIRI demonstrated improvement over FOLFIRI alone in the *K-Ras* wild-type population.

Erbitux shows improved OS, PFS, and ORR in *K-Ras* wild-type population.

Summary

- Accelerated approval in mCRC allowed patients access to Erbitux 3 years earlier than the traditional regulatory path.
  - Multiple studies were ongoing at the time of the accelerated approval
  - Sponsor encountered challenges including changes in SOC, impact of Erbitux availability on survival results, and evolving science
  - Ongoing dialogue with the FDA
  - Confirmed clinical benefit of Erbitux as a single agent in mCRC

FDA and Sponsor agreed on a path forward to complete conversion of accelerated approval to regular approval.